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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/014,670
Filing Date: December 14, 2001
Appellant(s): SUBTIL ET AL.

SUBTIL ET AL.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 20, 2007 appealing from the Office action mailed February 1, 2007.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of invention contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the issues in the brief is correct.

(7) Claims Appendix

Appellant's copy of the appealed claims contained in the appendix is correct.

(8) *Evidence Relied Upon*

Demers et al *(WO 9958714 published November 18 , 1999).*

Graffais et al *(U.S. Patent No. 6,559,294 issued May 6, 2003).*

Kalman et al *(Nature Genetics, Vol. 21, April 1999).*

Stephens et al *(U.S. Patent No. 6,822,071 issued November 23, 2004).*

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 7-10, 34-37 and 44-47 are rejected under 35 U.S.C. 103(a) as unpatentable over Graffais et al *(U.S. Patent No. 6,559, 294 B1 published May 6, 2003)* in view of Demers et al *(WO 99/58714, published November 18, 1999)* and further in view of Kalman et al *(Nature Genetics, Volume 21, April 1999).*

Claims 7-10, 34-37 and 44-47 are drawn to a method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the peptide of interest, (b) transforming a Gram-negative strain containing a type III secretion pathway with said

recombinant vector; (c) expressing said vector in said Gram-negative transformed strain; and (d) detecting the secretion of said DNA expression product; wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide.

Graffais et al teach a method of identifying a secreted *Chlamydia polypeptide* comprising using a vector and or cell transformed with said vector and /or transgenic animal comprising one or more transformed cells containing nucleotide sequence encoding a *Chlamydia pneumoniae* secreted polypeptide involved in a type III secretion pathway (columns 50 and 51). Graffais et al teach that the vectors of the invention comprise the elements necessary to allow expression and/or secretion of said nucleotide sequences in a give host (column 46). Graffais et al teach that a preferred host cell for the expression of the proteins of the invention is a gram-negative bacteria (column 48). Graffais et al teach that detection of secreted polypeptides can be detected by techniques known in the art (column 40).

Graffais et al do not teach the claim limitation "wherein said gram-negative strain containing a type III secretion pathway is a *Shigella* strain".

Demers et al teach that *Shigella* bacteria are gram-negative organisms that contain type III secretion machinery (page 1).

Demers et al nor Graffais et al teach *Chlamydia* polypeptides selected from the group consisting of CPn0105, CPn0287, CPn0330, CPn0334 CPn374, CPn379, CPn705, CPn0710, CPn0711, CPn0820, CPn821, CPn1016 and CPn1022.

Kalman et al teach *Chlamydia* polypeptides from *Chlamydia pneumoniae* and *C. trachomatis* genomes (see the Title). Kalman et al teach for example, CPn0105 (CT016) which is a GcpE protein that is conserved in both the *Chlamydia pneumoniae* and *C. trachomatis* genomes (Table 1, page 5). Kalman et al teach that comparative analysis of the *Chlamydia pneumoniae* and *C. trachomatis* genomes will significantly enhance the understanding of both pathogens and identification of genes shared between the two species supports the requirement for capabilities in biological systems that have, over long-term association with mammalian cells, evolved to reduce metabolic capacities while optimizing survival, growth and transmission of these unique pathogens (page 385).

It would be *prima facie* obvious at the time the invention was made to identify polypeptides as taught by Kalman et al using the method of identifying polypeptides using Type III secretion machinery as combined above because Graffais et al teach that secreted *Chlamydia* polypeptides identified using vectors and/or cells transformed with said vector and /or transgenic animal comprising one or more transformed cells containing nucleotide sequence encoding a *Chlamydia pneumoniae* secreted polypeptide involved in a type III secretion pathway. It would be expected barring evidence to the contrary, that identifying *Chlamydia* polypeptides would significantly enhance the understanding of *Chlamydia* pathogens and identification of genes shared between the two *C. pneumoniae* and *C. trachomatis* which enhance the understanding of both pathogens as well as be important in terms of virulence and pathogenesis capabilities of each pathogen.

II. Claims 7-10, 34-37 and 44-47 are rejected under 35 U.S.C. 103(a) as unpatentable over Stephens et al *(U.S. Patent No. 6,822,071 B1 published November 23, 2004)* in view of Demers et al *(WO 99/58714, published November 23, 2004).*

Claims 7-10, 34-37 and 44-47 are drawn to a method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the peptide of interest, (b) transforming a Gram-negative strain containing a type III secretion pathway with said recombinant vector; (c) expressing said vector in said Gram-negative transformed strain; and (d) detecting the secretion of said DNA expression product; wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide.

Stephens et al teach a method of identifying a secreted *Chlamydia polypeptide* comprising using a vector and transforming the cells into host cells (columns 15 and 16). Stephens et al teach that the vectors of the invention comprise the elements necessary to allow expression and/or secretion of nucleotide sequences in a host (column 16). Stephens et al teach that such bacteria host cell such as *E. coli* can be used for the expression of the proteins of the invention (column 16). Stephens et al teach that detection of *Chlamydia* gene expression can be performed in a variety of ways (column 15). Stephens et al teach a secreted protein, for example, CPn105 (CT016)(a polypeptide of the elected species) (see Table 2, columns 27-28).

Stephens et al do not teach the claim limitation "wherein said gram-negative strain containing a type III secretion pathway is a *Shigella* strain".

Demers et al teach that gram-negative bacteria contain type III secretion machinery and can secrete proteins via this machinery (pages 1 and 2). Demers et al teach that *Shigella* species can be used to secrete proteins (pages 1 and 6-9).

It would be *prima facie* obvious at the time the invention was made to modify the method of identifying *Chlamydia* polypeptides as taught by Stephens et al by using the Type III secretion machinery of Shigella to secrete a desired *Chlamydia* polypeptide because Demers et al has teach that polypeptides can expressed using the type III secretion pathway of gram-negative bacteria (e.g. *Shigella* species). It would be expected barring evidence to the contrary, that the type III secretion pathway of *Shigella* would be effective in secreting *Chlamydia* polypeptides.

(10) Response to Arguments

I. Response to Arguments Traversing the Rejection of claims 7-10, 34-37 and 44-47 under 35 U.S.C .103(a).

Appellants Specific Arguments Restated

A) Appellant urges that the claimed invention is an entirely different method of identifying secreted *Chlamydia* proteins compared to what is describe or suggested by the combination of cited art. Appellant urges that Demer et al describe screening for agent/compounds that change the expression of the type III secretory proteins and/or which block secretion through this pathway.

Appellant urges that Graffais et al describe a number of *Chlamydia* proteins some of which are characterized as Type III secreted proteins. Appellant urges that the teaching of Graffais et al is not focused on this rather disclose the genes and then go on to describe that the genes and their corresponding proteins could be used for almost any imaginable use of such molecules, e.g. hybridization, eliciting an immune response, identifying compounds which block pathgenesis and others.

B) Appellant urges that Kalman et al is merely cited for the proposition that certain *Chlamydia* genes were known but does not add anything in the method as claimed.

Appellant urges that the Office's rejection lacks merit for two reasons:

(1) one would not have used Demers et al secretion system as alleged by the Office because doing so would contrary to what is taught (KSR does not modify the notion that if art teaches NOT to do something then obviousness still exists). Demers et al is directed to looking for agents that block secretion or change the expression patterns NOT for determining whether a certain *Chlamydia* protein is one that can be secreted though the type III pathway.

(2) Appellant urges that the cited art provides no reason to believe that the expression of *Chlamydia* would, in fact, work in other gram negative strains such as Shigella. Appellant urges that the Office draws a conclusion that is not supported by facts.

Appellant urges that, heterologous secretion of a secreted *Chlamydia* polypeptide can be obtained only if the signal of the *Chlamydia* polypeptide is identical to the signal of the bacteria in which the secretion is tested. Appellant urges that this

was not obvious for *Shigella* first because the signal is still unknown and second because of the phylogenic distance of Chlamydia with other organisms.

Appellant urges that many secreted proteins need to be secreted together with a chaperone protein. Appellant refers to Examples in the literature such as Parot et al, Curr Opin Microbiol 2003 Feb, 6(1):7-14, Tuckerdagger and Galan, J Bacteriol., 2000 Apr;182(8);2262-8, Fields et al J Bacteriol., 2005 Sep;187(18):6466-78 and Slepenkin et al J Bacteriol, 2005, Jan;187(2):473-9.

II. Appellant urges that neither Stephens et al nor Demers et al describe a method for identifying secreted proteins but rather the general methodology for expressing proteins. Appellant urges that it must be understood that expression of a protein and secretion of the same are not necessarily the same thins , e.g. protein can be expressed without also being secreted.

Appellant urges that Demers et al describe screening for agents/compounds that change the expression of type III secretory proteins and/or which block secretion through this pathway.

Appellant urges that heterologous secretion of a secreted *Chlamydia* polypeptide can be obtained only if the signal of the *Chlamydia* polypeptide is identical to the signal of the bacteria in which the secretion is tested.

Appellant urges that this was not obvious for *Shigella* first because the signal is still unknown and second because of the phylogenic distance of *Chlamydia* with other organisms.

Examiner's Response to Appellant's Arguments

I. Applicant's arguments filed December 20, 2007 have been fully considered but they are not persuasive.

A) It is the Examiner's position that the combination of references teach the claimed invention. One of ordinary skill in the art would be motivated to combine the prior art references because Demers et al teach a method of screening polypeptides using the type III secretion machinery of gram-negative bacteria. Appellant urges that Demers describes screening for agent/compounds that change the expression of type III secretory protein and/or which block secretion through this pathway. Graffais et al teach that *Chlamydia* polypeptides can be secreted by the type III secretion machinery and Kalman et al disclose the specific *Chlamydia* polypeptides that can be secreted by the type III secretion machinery of gram-negative bacteria. One of ordinary skill in the art would reasonably conclude that specific *Chlamydia* polypeptides can be identified by using the type III secretion machinery of gram-negative bacteria and that these polypeptides can be detected using techniques known in the art based on the combination of prior art references.

It should be noted that *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a

person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use the type III machinery found in bacteria to identify and detect molecules. See Demers et al, see entire document and Griffais et al, see column 40. Kalman et al teach specific *Chlamydia* proteins that are known in the art. See Kalman et al, entire document. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness.

B) To address Appellant's comments regarding Demers et al, Demers et al teach screening or identifying compounds by the in use of gram-negative type III secretion machinery (pages 2-3). The method steps include exposing the gram-negative bacterial cells to sample molecule wherein the bacterial cells contain a reporter gene transcriptionally fused to a promoter of gene activated or regulated by the type III secretion machinery and detecting the presence or activity of the product of the reporter gene. It should be noted that Demers et al teach method detecting molecules that *activate* (these molecules enhance secretion and do not block secretion).or inhibit secretion.

To address Appellant's comments regarding compatibility of other organisms or compatibility of type III machinery e.g. *Shigella*, Demers et al teach that *any gram-negative bacteria containing type III secretion machinery may be used in the methods of this invention.* Demer et al teach that suitable members of bacteria include *Shigella, Salmonella, Yersinia, Escherichia, Pseudomonas, Xanthomanas, Raistonia* and *Erwinia*. Based on the teaching of the prior art one of ordinary skill in the art would reasonably conclude that *Chlamydia* proteins can be secreted via the type III machinery of other gram negative organisms. Therefore, the type III machinery in these gram-negative organism is compatible.

To address the reference submitted by Appellant (Parsot, Tuckerdagger, Fields et al and Slepenkin et al), it should be noted that these references have been submitted to point out the necessity of co-expressing a chaperone protein to get secretion in *Salmonella* or the presence of functional chaperone protein *Chlamydia.* While it is true that chaperones play various roles in functions associated with the secretion of proteins it should be remembered that the method as disclosed in the combined teachings of the prior art would allow one of ordinary skill to identify secreted *Chlamydia* polypeptides via gram-negative type III machinery.

II. Appellant's arguments filed December 20, 2007 have been fully considered but they are not persuasive.

It is the Examiner's position that the combination of references teach the claimed invention. One of ordinary skill in the art would be motivated to combine the prior art

references because Stephens et al teach a method of identifying a secreted *Chlamydia polypeptide* comprising using a vector and transforming the cells into host cells (columns 15 and 16). Stephens et al teach that detection of *Chlamydia* gene expression can be performed in a variety of ways (column 15). Stephens et al teach a secreted protein, for example, CPn105 (CT016)(a polypeptide of the elected species) (see Table 2, columns 27-28). Stephens et al do not teach that the expression product is secreted by *Shigella.* However, Demers et al teach a method of screening polypeptides using the type III secretion machinery of gram-negative bacteria, such as *Shigella.* One of ordinary skill in the art would reasonably conclude that specific *Chlamydia* polypeptides can be identified by using the type III secretion machinery of gram-negative bacteria and that these polypeptides can be detected using techniques known in the art based on the combination of prior art references.

It should be noted that *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use the type III machinery found in gram-negative bacteria to identify and detect molecules. See Demers et al, see entire document. Stephens et al teach methods of identifying secreted *Chlamydia* polypeptides and Stephens et al also teach specific

Chlamydia proteins that are known in the art. See Stephens et al, entire document. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness.

To address Appellant's comments regarding Demers et al, Demers et al teach screening or identifying compounds by the in use of gram-negative type III secretion machinery (pages 2-3). The method steps include exposing the gram-negative bacterial cells to sample molecule wherein the bacterial cells contain a reporter gene transcriptionally fused to a promoter of gene activated or regulated by the type III secretion machinery and detecting the presence or activity of the product of the reporter gene. It should be noted that Demers et al teach method detecting molecules that *activate* (these molecules enhance secretion and do not block secretion).or inhibit secretion.

To address Appellant's comments regarding compatibility of other organisms or compatibility of type III machinery e.g. *Shigella*, Demers et al teach that *any gram-negative bacteria containing type III secretion machinery may be used in the methods of this invention.* Demer et al teach that suitable members of bacteria include *Shigella, Salmonella, Yersinia, Escherichia, Pseudomonas, Xanthomanas, Raistonia* and *Erwinia*. Based on the teaching of the prior art one of ordinary skill in the art would reasonably conclude that *Chlamydia* proteins can be secreted via the type III

machinery of other gram negative organisms. Therefore, the type III machinery in these gram-negative organisms is compatible.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Examiner's Answer Conclusion

For the above reasons, it is believed Examiner should be affirmed.

Respectfully submitted,

/Vanessa L. Ford/

Examiner, Art Unit 1645

April 13, 2008

Conferees

/Shanon A. Foley/
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